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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/234,208	01/20/1999	JONI KRISTIN DOHERTY	49321-1	6406

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EXAMINER
HUNT, JENNIFER ELIZABETH

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 05/22/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/234,208	Doherty et al.
Examiner	**Art Unit**
Jennifer Hunt	1642

-- The MAILING DATE of this c mmunication appears on the c ver sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Feb 1, 2002* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-3, 8-10, and 18-20* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-3, 8-10, and 18-20* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Response to Amendment

1. Acknowledgment is made of applicant's cancellation of claims 4-7, 11-17, and 21-26. Claims 1-3, 8-10, and 18-20 are pending in the application and considered herein.

2. The text of Title 35 of the U.S. Code not reiterated herein can be found in the previous office action.

3. This action contains new grounds of rejection and thus is a non-final action.

Claim Rejections and Objections Withdrawn

4. The objection to the specification for use of the trademark Herceptin(R), and Brightstar (R) is withdrawn in light of the amendments thereto.

5. The rejection of claims 1-3, 8-10, and 18-20 under 35 U.S.C. 112, second paragraph, as unclear in the recitation of "extracellular domain ECD" is withdrawn in light of the amendments thereto.

6. The rejection of claims 1-3, 8-10, and 18-20 under 35 U.S.C. 112, second paragraph as reciting the relative term "10^{8}" is withdrawn in light of the amendments thereto.

7. The rejection of claims 3 and 10 for reciting the trademark/trade name HERCEPTIN (R) is withdrawn in light of the amendments thereto.

The rejection of claims 1-3, 8-10, and 18-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated peptide comprising

SEQ ID NO:1, or SEQ ID NO:2, does not reasonably provide enablement for any isolated peptide having from about 50-79 or 69-79 amino acids taken from SEQ ID NO:1, or from about 80-419, or 300-419 or about 350-419 amino acids from SEQ ID NO:2 is withdrawn in light of the amendments thereto.

8. The previous grounds of rejection of claims 18-20 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, with regard to antibodies which bind to an epitope which is at least in part distinct from the epitope bound by the Herceptin antibody is withdrawn in light of the new grounds of rejection set forth below.

Claim Rejections Maintained/New Grounds of Rejection

9. Claims 3 and 10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 3 and 10 are unclear in the recitation of a site that is "at least in part distinct." The metes and bounds of "at least in part distinct: cannot be determined. It is not clear what would be considered "at least in part distinct" and what would not.

10. Claims 1-3, 8-10, and 18-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated peptide comprising SEQ ID NO:1, or SEQ ID NO:2, does not reasonably provide enablement for any isolated peptide having from about 50-79 or 69-79 amino acids taken from SEQ ID NO:1, or from about 80-419, or about 350-419 amino acids from SEQ ID NO:2 which bind to the extracellular domain of HER-2, including peptides which further do not bind to the epitope bound by HERCEPTIN. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining scope and enablement are: 1) quantity of experimentation necessary, 2) the amount of direction or guidance presented in the specification, 3) the presence or absence of working examples, 4) the nature of the invention, 5) the state of the prior art, 6) the relative skill of those in the art, 7) the predictability of the unpredictability of the art, and 8) the breadth of the claims (see Ex parte Forman, 230 USPQ 546, BPAI, 1986).

The claims are broadly drawn to any isolated peptide which has about 50-79 or 69-79 amino acids taken from SEQ ID NO:1, or from about 80-419, or about 350-419 amino acids taken from SEQ ID NO:2, which binds to the extracellular domain of HER-2. Further, claims 3 and 10 are drawn to any such peptide which binds to a site that is at least in part distinct from the site of binding of HERCEPTIN. Thus to meet the limitations of the claims, the peptides must bind to a specific region of the HER-2 peptide.

The specification discloses a single isolated polypeptide, p68HER-2, which comprises a modified extension of the art known p185HER-2, which is a 79 amino acid peptide, named ECDIIIa. Both p68HER-2 and ECDIIIa bind to p185HER-2 and do not activate signal transduction. The specification provides no objective evidence that any other isolated polypeptides which would function as ECDIIIa and p68HER-2 do.

The specification provides no guidance or objective evidence that the claimed isolated polypeptide binds to a site other than that bound by the HERCEPTIN antibody. Further, applicant has given no guidance (beyond a generic teaching) as to what the HERCEPTIN antibody refers to, or where that antibody binds. The instant disclosure fails to clearly set both where the antibody binds, how the antibody is produced, or any of the structural or functional information which would be necessary to produce the antibody, or determine how to produce a polypeptide which binds to a distinct site. Further, there is no evidence or guidance that the ECDIIIa or p68HER-2 peptides themselves bind to a site other than the one bound by the HERCEPTIN antibody.

Furthermore, predicting which epitopes are bound by a particular peptide, or further speculating as to how to develop an antibody which binds to a specific epitope, or alternatively binds to any epitope except a specific disclosed epitope is established in the art to be unpredictable. As taught in Greenspan et al (Nature Biotechnology 7:936-937 (1999)) defining epitopes is not as easy as it seems (page 937). Epitopes have been defined in terms of the spacial organization of residues that make contact with a ligand and the structural characterization of the

molecular interface for the binding of the molecules to define the epitope boundaries (page 937 middle of page). The epitope defined in this manner will likely include residues that contact the ligand but are energetically neutral or even destabilizing to binding. "In addition, a priori it will not include any residue that makes no contact with a ligand but whose substitution may profoundly effect ligand recognition through influence on the stability of the free form of the macromolecule, or participation in long-range allosteric effects". "Even when the residues making contacts with ligand are known with certainty, say from the crystal structure of the complex, the question remains with regard to the energetic involvement of each residue (page 936 right column, first paragraph). Therefore, "amino acids should be recognized to have multiple ways of contributing to a noncovalent interaction" (page 937, middle of page). As evidenced by Greenspan et al a number of factors not primarily related to the contours of the contacts of the molecules contribute to the free energy change, sometimes profoundly.

Thus because the quantity of experimentation necessary would be very high and the predictability of the art is low, the amount of direction or guidance presented in the specification is low, there are no working examples, and the claims are broadly drawn, one of skill in the art would not be able to make the invention commensurate in scope with the claims.

11. The rejection of claims 18-20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make

and/or use the invention, as it pertains to pharmaceutical compositions is maintained for reasons of record.

The claims are broadly drawn to any isolated peptide which has about 50-79 or 69-79 amino acids taken from SEQ ID NO:1, or from about 80-419, or 300-419 or about 350-419 amino acids taken from SEQ ID NO:2, which function as a pharmaceutical composition.

The claims recite methods which encompass the experimental and unpredictable field of in vivo therapy for mammals having a condition characterized by over expression of Her-2 receptor or cancer. Articles by Dillman et al. (*J Clin Onco Vol 12, No 7, pages 1497-1515, 07/1997)* and *Dermer (BIO/TECHNOLOGY, Vol 12, page 320, 03/1994*) are cited in order to establish the general state of the art and the level of predictability of in vivo therapy . Dillman et al, while discussing observations related to antibody therapy, teach that "on the negative side is the observation that clinical results do not necessarily improve when humanized chimeric antibodies are used in humans, to spite encouraging in vitro results in CDC or ADDC" (page 1506, col 2 paragraph 3). Dermer teaches that "What is significant in culture, for example immunotherapy's killing power or the transformation of 3T3 cells by a mutated proto-oncogene, simply does not have the same significance for cells in vivo."

Those of skill in the art recognize that in vitro assays are generally useful to screen the effects of agents on target cells. However, clinical correlations are generally lacking. The greatly increased complexity of the in vivo experiment as compared to the very narrowly defined and controlled conditions of an in vitro assay does not permit a single extrapolation of in vitro assays

to mammal or human therapeutic with any reasonable degree of predictability. In vitro assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Further a therapeutic agent must accomplish several tasks to be effective: it must be delivered into circulation and interact at the proper site of action, and it must do so at a therapeutic concentration and remain effective for a sufficient period of time. In vitro assays cannot duplicate the complex conditions of in vivo therapy. In assays, the agent is in contact with the cells during the entire exposure period, whereas in the case of in vivo therapy, exposure at the target site may be delayed or insufficient.

Further, applicant has demonstrated no anti-tumor function of the ECDIIIa or p68HER-2 polypeptides themselves, nor the additional numerous peptides encompassed by the broadly drawn claims. Applicant's disclosure shows that the ECDIIIa or p68HER-2 polypeptides bind to the p185HER-2 polypeptide, and do not activate signal transduction, but applicant has provided no further guidance or evidence of anti-tumor activity, or even why one of skill in the art would expect such a function to induce anti-tumor activity.

The field of cancer therapy is well established to be highly complex and unpredictable, and absent specific guidance or objective evidence, one of skill in the art would not expect a polypeptide to have an anti-tumor function. Further, it is known in the art that anti-HER-2 antibodies function unpredictably with regard to pharmaceutical effect.

Further it is established in the art that antibodies to the ErbB2 receptor exhibit highly variant activity. For example, Xu et al., Int. J. Cancer, Vol. 53, pages 401-408, 1993 described a

panel of 10 anti-HER2 Mab's which exhibit distinct binding characteristics and activities (see abstract). Also, Shepard et al., Journal of Clinical Immunology, Vol. 11, No. 3, 1991, pages 117-126 describes a panel of 9 anti-HER2 Mab's which exhibit distinct binding characteristics and activities (see pages 119-120.

Thus because the quantity of experimentation necessary would be very high and the predictability of the art is low, the amount of direction or guidance presented in the specification and the working examples in the specification are limited, and the claims are broadly drawn, one of skill in the art would not be able to make the invention commensurate in scope with the claims.

Applicant argues that the specification provides support for pharmaceutical compositions at page 13, lines 5-23 of the specification, and at Figure 7, citing an in vitro assay of tumor cytotoxicity, and further citing 3 references as support that this model is predictive of tumor cytotoxicity. Applicant further argues that ECDIIIa and p68HER-2 act by preventing activation of the HER-2 receptor and thus would be expected to have anti-tumor cell activity. Applicant's arguments filed February 1, 2002 have been fully considered but are not persuasive.

The sections of the specification cited by applicant refer to a general discussion of therapeutic potential, and to an in vitro assay. The references cited by applicant as supportive of this model were not included with the response. As set forth in the previous office action, the disclosure of one in vitro test is not commensurate in scope with an alleged pharmaceutic function, particularly in light of the unpredictable nature of the art. Further, the contention that

ECDIIIa and p68HER-2 act by preventing activation of the HER-2 receptor and thus would be expected to have anti-tumor cell activity is not predictable, in light of the lack of predictability of the effect of receptor interactions on tumor activity set forth above, and the lack of guidance with regard to the mechanisms and pharmaceutical effect of these interactions. Specifically, it is not clear that ECDIIIa and p68HER-2 do block activation of HER-2, sufficient to produce a pharmaceutical effect.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Hunt, whose telephone number is (703) 308-7548. The examiner can normally be reached Monday through Thursday 6:30am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached at (703) 308-3995. The fax number for the group is (703) 305-3014 or (703) 308-4242.

Communications via internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [**anthony.caputa@uspto.gov**].

All internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists the possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the group receptionist, whose telephone number is (703) 308-0196.

Jennifer Hunt

May 19, 2002

SHEELA HUFF
PRIMARY EXAMINER